THERAPEUTIC ADVANCES in
Gastrointestinal Endoscopy

Original Research

Evaluation of the sedative effect of sublingual lorazepam *versus* placebo in patients underwent endoscopy: a double-blind, randomized controlled clinical trial

Ther Adv Gastrointest Endosc

2023, Vol. 16: 1–10

DOI: 10.1177/26317745231219597

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Abstract

Background: Digestive endoscopy (DE) is uncomfortable for most patients. Lorazepam is a potent benzodiazepine with anxiolytic and sedative effects.

Objective: This study aims to determine the sedative effect of sublingual lorazepam *versus* placebo as a premedication in patients who underwent DE.

Design: This is a mono-center, double-blind, and randomized controlled trial.

Methods: A lorazepam sublingual tablet was made by researchers and physical tests were done on it, then the double-blind placebo-controlled trial was done to investigate the efficacy of 2 mg sublingually administered lorazepam as a premedication for endoscopy. Lorazepam or a placebo tablet was administered sublingually 30 min before the endoscopy. The patients, nurses, and physicians were blinded to the patient group. The depth of sedation was evaluated according to the American Society of Anesthesiology.

Results: In all, 116 patients were randomly assigned to take either lorazepam ($n = 58$) or a placebo ($n = 58$). The results of physical properties tests were acceptable according to United States Pharmacopeia. There were no statistical differences between groups regarding age and gender. In the lorazepam group, 75.8% of patients showed mild sedation, and 24.2% of patients showed no sedation. All of the patients in the placebo had no sedation ($p = 0.001$). Time of procedure ($p < 0.001$), intraoperative O_2 saturation ($p < 0.001$), intraoperative heart rate ($p < 0.001$), and intraoperative blood pressure ($p < 0.001$) were significantly lower in the lorazepam group. No significant or dangerous side effects were observed except a bit of giddiness and dizziness.

Conclusion: The results of this study showed that prescription of sublingual lorazepam 25–30 min before endoscopy provided mild sedation.

Registration: IRCT201611039014N130 (05/11/2016); https://en.irct.ir/trial/9568.

Keywords: endoscopy, lorazepam, premedication, sublingual

Received: 30 March 2023; revised manuscript accepted: 9 November 2023.

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Introduction

Digestive endoscopy (DE) is an essential diagnostic and therapeutic approach in gastroenterology. DE may be performed both in outpatient and in-hospital sections. This procedure can be performed with or without sedation; however, some patients do not tolerate the procedure without sedation. Although sedation makes the DE

more tolerable, it may be associated with cardiac or respiratory adverse events, particularly in patients with pulmonary heart diseases.[1]

The ideal desirable sedative agent should provide a predictable rapid onset of effect and recovery without accumulation, tachyphylaxis, or withdrawal symptoms. Any cardiopulmonary insult and toxicity should be avoided by an appropriate approach for sedation[2]; however, given the limited access to general anesthesia in many centers, a significant proportion of patients undergo endoscopies under intravenous sedation.[3]

Oral administration of sedative agents as premedication is potentially an alternative to intravenous administration of such medication for patients undergoing gastrointestinal endoscopic procedures. The sublingual route is known as an alternative path for drug administration. Oral mucous membrane with its high vascularity accelerates drug absorption providing rapid onset of action, bypassing the first-pass metabolic process of the liver with more bioavailability of the drug; therefore, the low dosage makes high efficacy and decreased risk of side effects and increased patients' compliance and satisfaction.[4]

Although propofol was shown to be the most effective sedative for both adults[5] and children,[6] benzodiazepine opioid combinations also remain prevalent.[6] Benzodiazepines are known for their anti-anxiety, hypnotic, muscle relaxant, and anticonvulsant effects. They accelerate the fixation of gamma-aminobutyric acid (GABA) on GABA type A receptors and increase the inhibitory properties of GABA.[7] Prescribing benzodiazepines to older patients can lead to risks such as lethargy, confusion, falls, impaired driving, and emergency room visits, and long-term benzodiazepine use fosters dependence and exposure to potentially serious consequences, such as withdrawal-induced delirium, seizures, and death. Also, there is evidence that long-term use of benzodiazepines will increase the risk of dementia.[8,9]

Among benzodiazepines, previous studies have shown that oral midazolam is effective as a premedication; however, it is not widely available and has a higher cost than other benzodiazepines. In addition, oral midazolam has been associated with some side effects such as respiratory depression and hypotension.[10] Lorazepam is a newer generation of benzodiazepines with high potency. It has low lipid solubility, with slow blood–brain barrier passage or passing. So has delayed onset with a longer duration of action.[11]

Lorazepam is eliminated by direct liver glucuronidation, and its inactive metabolites are excreted in the urine. While the onset of effect and half-life of lorazepam is not ideal, it has a shorter half-life between the benzodiazepines and an anterograde amnesic effect, which is a pleasant effect for the patients. Besides that, lorazepam had a high partition coefficient with a high absorption rate, allowing sublingual administration[12]; also, lorazepam can be used in patients with hepatic dysfunction with insignificant effects on the pharmacokinetics.[13]

Consequently, lorazepam may be a suitable prodrug for sedation during DE. As far as we know, few studies have been conducted regarding the use of lorazepam for this purpose. Based on the characteristics of lorazepam, in this study, we determined and compared the efficacy of the standard sublingually formulation of lorazepam, in sedative effect during DE.

Methods and materials

Trial design

The DE-Lora study is a mono-center randomized, double-blind, placebo-controlled, and parallel trial that aims to assess the effectiveness of a single dose of sublingual lorazepam on sedative effect in patients undergoing a DE.

Participant eligibility criteria

This study was conducted in the endoscopy unit of Shahid Beheshti Hospital in Hamadan City (Iran) from January 2018 to February 2019. Adult patients with upper gastrointestinal complaints who were referred for elective DE were evaluated for entering the study. All patients underwent esophagogastroduodenoscopy and all indicated biopsies, also all DE were performed by the same operator.

Patients were entered into the study if this was their first experience with DE, their physical status was class 1 or 2 according to the American Society of Anesthesiology (ASA) system, and they were willing to participate.

Patients with the following conditions were not included in the trial: long-term use of

benzodiazepines, benzodiazepine consumption within 24 h before endoscopy, hypersensitivity to benzodiazepines, major psychiatric disorders (psychosis); disabling neurologic disorders (dementia, mental retardation), bodyweight > 100 kg or BMI > 30, severe cardiac or pulmonary diseases or other severe diseases interfering with conducting the study or outcome assessment, pregnancy, and lactation. In addition, patients who received drugs that interact with lorazepam [liver enzyme inhibitors (carbamazepine, phenobarbital, phenytoin, rifampin), valproic acid, probenecid, estrogen-containing oral contraceptives, central nervous system suppressants (alcohol, barbiturates, opioids), clozapine, levodopa, neuromuscular blockers] were excluded.

Patients with the following conditions during DE were excluded from the trial: the presence of gastrointestinal anomaly or stricture, the need for therapeutic endoscopic intervention, and active bleeding.

Intervention details

Preparation of mucoadhesive sublingual tablets. First, the carrier material [D-Mannitol (C6H14O6 MW = 2.182, Solarbio, China)] was mixed with the drug [Lorazepam (Abidi, Iran)] for 12 h using a cubic mixer (AR402, Kavosh, Iran), then with the filler [Avicel PH-102 (microcrystalline, Boehringer Mannheim, Germany)] and co-spraying material [Max-povidone A (Crospovidone type A, USP-37, HSH-Chemie, Germany)] were mixed for another 20 min, then the resulting powder was mixed with lubricant [magnesium stearate (stearic acid magnesium salt, light white powder, Boehringer Mannheim, Germany)] and turned into tablets with single punch tableting machine (Kavosh, Iran). The total weight of the tablet was considered to be 120 mg and it was compressed with an eight punch. The method of making a placebo is similar to sublingual lorazepam, with the difference that it contains 2 mg of Avicel instead of the drug.

Clinical trial. On the day of the procedure, patients in the sublingual lorazepam received one tablet of the standard oral formulation of lorazepam 2 mg (produced by the Hamadan School of Pharmacy, Hamadan, Iran) to consume sublingually 30 min before the procedure. Those in the placebo groups received placebo tablets (produced by the Hamadan School of Pharmacy, Hamadan, Iran) to consume sublingually at the same time point.

Allocation methods

Randomization. Participants were randomly allocated to the lorazepam or placebo group in the random blocks of four subjects (allocation ratio 1:1). Randomization was done by the blocked randomization method. A computer random number generator generated the sequence of permuted blocks. To decrease confounding factors and selection bias, randomization was done by one independent statistician.

Blinding. Patients, physicians, nurses, research assistants, and the statistician who analyzed the data were all blinded to the participant's allocation group. The placebo tablets were the same as the lorazepam in color, package, shape, and size.

Sample size calculation

According to Van der Bijl *et al.*'s study, which aimed to investigate the sedative effects of sublingual lorazepam compared to a placebo in oral surgery, it was found that the intervention group had a 90% recovery rate while the recovery rate of the placebo group was 65%. Based on this, the sample size required for a confidence level of 95% and a statistical power of 90% was calculated using the formula[14]; therefore, the sample size for each group will be 57 individuals and a total of 114 individuals

$$\bar{P} = \frac{P_1 + P_2}{2} = \frac{0.90 + 0.65}{2} = 0.775$$

$$n = \frac{\left[\begin{array}{l} Z_{1-\alpha/2}\sqrt{2\bar{P}\left(1-\bar{P}\right)} + \\ Z_{1-\beta}\sqrt{P_1\left(1-P_1\right)+P_2\left(1-P_2\right)} \end{array}\right]^2}{\left(P_1 - P_2\right)^2} =$$

$$\frac{\left[\begin{array}{l} 1.96\sqrt{2\times 0.775\times 0.225} + \\ 1.282\sqrt{0.90\times 0.10 + 0.65\times 0.35} \end{array}\right]^2}{\left(0.90 - 0.65\right)^2} = 57$$

Data collection

Tests performed on manufactured tablets. Various tests such as weight variation, content uniformity,

Table 1. Depth of sedation according to the American Society of Anesthesiology.

Depth	Definition
Minimal sedation (anxiolysis)	The patient answers normally to verbal orders Cognitive function may be diminished Ventilatory and cardiovascular functions are unaffected
Moderate sedation or analgesia (conscious sedation)	The patient responds purposefully to verbal commands with or without light tactile stimulation Spontaneous ventilation is acceptable Cardiovascular function is preserved
Deep sedation or analgesia	The patient is not easily aroused but responds purposefully to painful stimulation The patient may not be able to preserve a patent airway Spontaneous ventilation may be insufficient Cardiovascular function is usually continued
Anesthesia	Patients cannot be awakened, even by painful stimulation The patient often requires support in maintaining a patent airway Cardiovascular function may be impaired

hardness, assay, dimension, friability, disintegration time, and dissolution time were performed on manufactured tablets.

Weight variation of tablets: A total of 20 tablets were weighed and their mean and standard deviation were calculated according to United States Pharmacopeia (USP) standards.
Hardness: The hardness of six tablets was measured using a tablet hardness tester (Erweka GmbH, Germany).
Friability: The friability of six tablets was measured using a tablet friability tester (Erweka GmbH, Germany).
Assay: Ten tablets, equal to 5 mg of lorazepam, were ground into powder and added to 40 mL of ethanol. After being shaken for 1 h, the solution was diluted to 50 and 5 mL of this solution was diluted with ethanol to 100 mL. The absorbance was measured using a UV-Vis spectrophotometer (Analytikjena, Germany) at $\hat{I}max = 230$ nm. The procedure was performed in triplicate.
Content uniformity: This test was performed on three tablets separately so that one tablet was ground into powder and added to 40 mL of ethanol. The obtained solution was diluted to 50 mL after shaking for 1 h. Then, it was centrifuged and 1 mL of the supernatant was diluted to 10 mL and its absorbance was measured spectrophotometrically at 230 nm.
Dimensions of tablets: The thicknesses and diameters of five tablets were measured by a micrometer caliper (Guanglu, China).
Disintegration time of tablets: The disintegration time of six tablets was determined using a dissolution test instrument (Kavosh, Iran).
Dissolution test: The dissolution medium was 500 mL of phosphate buffer (pH 6.8) and dissolution instrument II of USP, that is, a rotating paddle was used at 50 rpm and 37.5 ± 0.5°C. Five milliliters of samples was taken at 1, 3, 5,7, and 10 min and replaced by 5 mL of phosphate buffer. After centrifugation of samples, the area under the curve with High-performance liquid chromatography (HPLC) analytical (LC20ADXR, Shimadzu, Japan) was measured. Finally, the cumulative percent of the dissolved drug was plotted *versus* time. This test was performed on three tablets.

Outcomes. Depth of sedation 30 min after administration of the drug was considered according to the ASA[15] and pain level [with St. Paul's endoscopy comfort score (SPECS)[16]] as the primary outcome (Table 1). The secondary outcome was determining the time of the procedure, preoperative and intraoperative O_2 saturation, blood pressure, and heart rate. The safety outcomes measures included the rate of any immediate or delayed adverse events in each group. For all procedures, blood pressure, heart and respiration

rates, peripheral oxygen saturation, and exhaled CO_2 were monitored. In addition, for safety outcomes, we contacted each participant 24–48 h after the procedure to assess the occurrence of any late adverse event.

Statistical analysis

Qualitative variables were reported as frequency and percentage. Quantitative variables were expressed as mean ± standard deviation (SD). Chi-square or Fisher's exact test was used to evaluate the possible associations among the qualitative variables, if appropriate. Parametric and nonparametric continuous variables were analyzed using paired sample *t*-tests, independent *t*-tests, Mann–Whitney *U* tests, and Wilcoxon, where applicable. *p* Values less than 0.05 were considered to be statistically significant. The analysis was conducted using SPSS 22 software (SPSS Inc., Chicago, IL, USA).

Results

Results of physical properties tests

Weight variation. The weights of all tablets were in the range of acceptable variations. According to the USP standards for tablets weighing less than 130 mg, the acceptable range is 10% of the mean weight and none of the formulations were out of this limit. The acceptable upper limit was 132 mg, and the acceptable lower limit was 108 mg because the weight of the tablets was changed to 120 mg. The mean ± SD weight (mg) of tablets was 125.22 ± 3.3 (Table 2).

Hardness. The mean ± SD of the hardness (*N*) for six tablets was 32.5 ± 2.28. A tablet hardness of about 3–4 kg (29.42–39.23 N) was considered adequate for mechanical stability[17] (Table 2).

Friability. The mean ± SD of friability (%) of six tablets was 3.83 ± 0.7. According to the USP, friability should be <1%. The results of the friability test according to USP were not acceptable in this study. However, according to the method of taking the medicine sublingually, this friability is not a problem in taking this medicine[18] (Table 2).

Assay. The amount of the active pharmaceutical ingredient (API) in three times of testing was within the USP range between 90% and 115% of the claimed amount (5 mg), which by converting to the amount of active ingredient in each tablet was in the range of 1.8–2.2 mg in 2 mg lorazepam tablets (Table 2).[18]

Table 2. Results of drug assessment.

Variable		Value
Friability (%)		3
Hardness (*N*) (mean ± SD)		32.5 ± 2.88
Weight variation (mg) (mean ± SD)		125.22 ± 3.3
Disintegration time (s) (mean ± SD)		6.5 ± 0.55
Dimension	Thickness (mm) (mean ± SD)	2.67 ± 0.016
	Diameter (mm) (mean ± SD)	8.03 ± 0.012
Content uniformity	Coefficient of variation (RSV)	5.3%
	(mean ± SD)	2.07 ± 0.11
API assay (mg) (mean ± SD)		2.25 ± 0.066

API, active pharmaceutical ingredient.

Content uniformity. The drug content in three assayed tablets was in the range of the standards of USP and was between 90% and 115% of the claimed amount and the CV% was less than 6%. The results of content uniformity are reported in Table 2.[18]

Dimensions of tablets. All tablets resulted in a mean ± SD diameter of 8.03 ± 0.012 mm and thickness of 2.67 ± 0.016 mm. These dimensions enhance drug absorption (Table 2).

Disintegration time of tablets. The mean ± SD of the disintegration time of tablets (s) for six tablets was 6.5 ± 0.55. A disintegration time of tablets of about 14 s was acceptable for sublingual drug[18] (Table 2).

Dissolution test. The percentage of released drugs was plotted *versus* time as seen in Figure 1.

Results of clinical trial

Demographics. A total of 162 patients were referred to our office during the study period, among whom 46 patients were not eligible for inclusion in the trial. Finally, a total of 116 patients were studied including 58 patients in

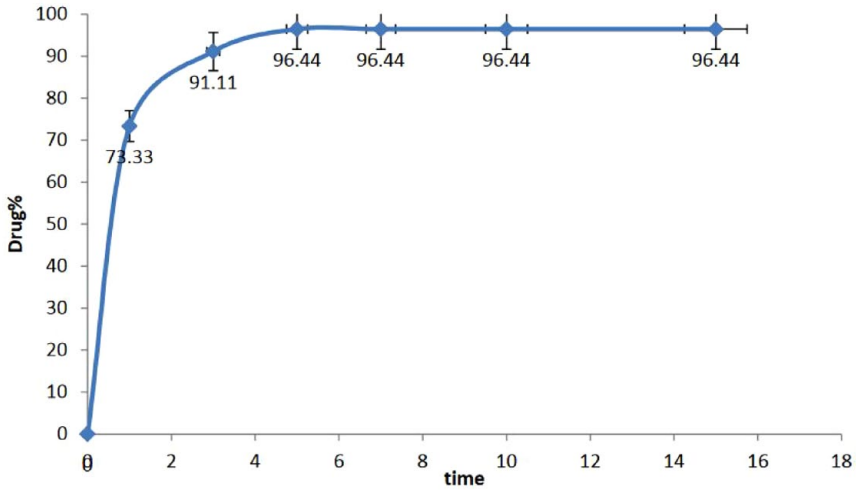

Figure 1. Sublingual lorazepam dissociation curve.

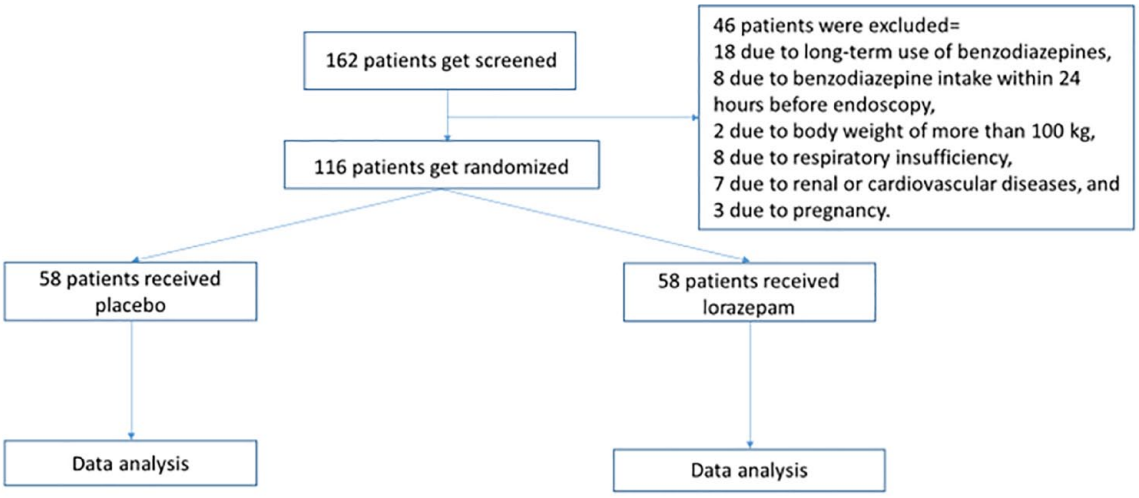

Figure 2. CONSORT diagram of the participants.

each group (Figure 2). The mean age in the lorazepam group was 45 ± 13 years and 53.5% were female and the mean age in the placebo group was 45 ± 13.4 years and 41.4% were female. There were no differences among the groups concerning demographic data (Table 3).

Primary outcome. The sedative effect of the premedication was evaluated by observational tests according to the ASA. The patient's anxiety, pain, level of consciousness, and cooperation were evaluated independently by the endoscopist and the anesthesiologist. In the lorazepam group, 75.8% of patients showed mild sedation and 24.2% of patients showed no sedation [inter-observer ICC = 0.958 95% CI (0. 0.932–0.983)].

All of the patients in the placebo had no sedation ($p = 0.001$) (Table 3). The pain level of patients in the lorazepam group was 1.01 ± 0.28 and in the placebo group was 1.13 ± 0.48 ($p = 0.024$) [inter-observer ICC = 0.964 95% CI (0.921–0.984)].

Secondary outcomes. According to Table 4, there was no statistically significant difference in preoperative O_2 saturation, heart rate, and blood pressure between the two groups. However, the time of procedure ($p < 0.001$), intraoperative O_2

saturation ($p < 0.001$), intraoperative heart rate ($p < 0.001$), and intraoperative blood pressure ($p < 0.001$) were significantly lower in the lorazepam group. Significant differences ($p < 0.05$) existed between the treatment group and placebo group for the sedative effect; therefore, this drug had a good sedation effect as premedication before endoscopy (Table 4).

Safety outcome. No immediate side effects were seen in patients; however, in 10 patients (17.2%) of the intervention group, giddiness and dizziness for about half an hour were observed.

Table 3. The baseline characteristics of participants and the effect of lorazepam on sedation.

Variable		Placebo	Lorazepam	*p* Value
Age (mean ± SD)		45 (13.4)	45 (13.0)	0.949
Gender	Female (%)	24 (41.4)	31 (53.5)	0.193
	Male (%)	34 (58.6)	27 (46.5)	
Sedation	No sedation (%)	58 (100)	14 (24.2)	0.001
	Mild sedation (%)	0 (0.0)	44 (75.8)	

Discussion

According to the results of our study, the administration of sublingual lorazepam was safe and effective as premedication of DE. It can diminish pain, anxiety, and discomfort associated with DE. Prescribing suitable sedatives before endoscopy can reduce patient discomfort and increase patient tolerance, satisfaction, and willingness to repeat the DE, which is essential for follow-up procedures. In addition, increasing the tolerance led to lessening the procedure time. Moreover, an effective sedative agent can decrease the need for intravenous sedation.[19]

Benzodiazepines are used widely as sedative drugs in endoscopic procedures. The intravenous route is the most effective way to administer benzodiazepines; however, it needs close patient monitoring, complete equipment, and expert nurses to deal with probable side effects.[20] Oral and sublingual administration are alternative routes and possibly will be a cost-effective method. Previous investigations have revealed that these routes can decrease anxiety and discomfort related to the operation and upsurge the tolerance and satisfaction of the patients.[19]

Sublingual administration of benzodiazepine causes a more rapid onset of action due to the high permeability and capability of the sublingual oral mucosa. Due to the low thickness and degree of keratinization of sublingual mucosa, sublingual delivery provides a high bioavailability rate. Previous studies reported the bioavailability of sublingual lorazepam about 94%.[21]

The results of the weight variation, content uniformity, assay, disintegration time, and dissolution were completely desirable according to USP. Although, the hardness test according to USP, the hardness of the tablets should be more than

Table 4. Time of procedure and preoperative and intraoperative O_2 saturation, heart rate, and blood pressure.

Variables	Drug				*p* Value	Cohen's d	95% confidence interval of Cohen's *d*	
	Lorazepam		Placebo					
	Mean	SD	Mean	SD			Lower	Upper
Time of procedure	7.7	1.3	8.7	1.8	<0.001	−0.657	−1.030	−0.282
Preoperative O_2 saturation	98.16	0.81	97.86	0.89	0.066	0.345	−0.023	0.710
Intraoperative O_2 saturation	96.79	1.25	97.59	1.11	<0.001	−0.670	−1.043	−0.295
Preoperative heart rate	91.22	12.71	94.60	8.31	0.093	−0.315	−0.680	0.052
Intraoperative heart rate	88.48	11.96	102.22	9.59	<0.001	−1.268	−1.665	−0.866
Preoperative blood pressure	10.54	1.55	10.78	1.35	0.391	−0.160	−0.524	0.205
Intraoperative blood pressure	10.31	1.50	11.34	1.41	<0.001	−0.705	−1.079	−0.329

40 Newtons, in this study, the mean hardness of the manufactured tablets was 32.5; however, according to Shailesh *et al.*'s study, the tablet hardness of about 3–4 kg, equivalent to 29.39–23.42 Newtons, was considered sufficient for the mechanical stability of the tablet.

In line with our study, in the study of Ahmad Shavakhi *et al.*, the administration of 0.5 mg sublingual lorazepam is an effective premedication for sedation during DE. It reduces anxiety and pain/discomfort related to DE and increases patient tolerance and willingness to repeat the DE if necessary.[10] Also, the study by Van der Bijl *et al.* was among the first investigations on sublingual lorazepam. The authors compared the sedative effect of sublingual lorazepam with intramuscular diazepam in maxillofacial surgery. They gave 2 and 3 mg sublingual lorazepam tablets to patients regarding their weight (below and above 50 kg, respectively). They stated that sublingual lorazepam showed the desired sedative and anxiolytic effect but it was associated with more significant side effects, such as dizziness, ptosis, and lengthy psychomotor impairment; however, in our study except for giddiness and dizziness, no other side effects were observed.[14]

On the other hand, some studies mentioned that lorazepam does not enhance postoperative stress and anxiety in patients. In Fella Chennou *et al.*'s study of 101 children undergoing DE, although sublingual lorazepam did not affect patients' preoperative stress, as measured by salivary cortisol; however, it was associated with a higher rate of comfortable procedures and temporary tachycardia was the most common intraoperative side effect in the lorazepam group.[6] Also, a randomized, double-blind trial was conducted to assess the sedative effect and enhancement in sedation quality of 1 mg orally administered lorazepam in patients who underwent endoscopic retrograde cholangiopancreatography. Their results did not show the beneficial effects of lorazepam as premedication. Incredibly, the dose of sedative drugs was higher in patients who received lorazepam.[22]

Strengths and limitations

The most important limitations of the present study were the investigation of a single dose of sublingual lorazepam and there is no comparison with other sedative agents to prove benzo use is superior without side effects, also the comparison of benzo dosing and weight-based changes to dosing needs further investigation. On the other hand, our study had some strengths. We recorded hemodynamic parameters during endoscopy. The allocation of patients in this study was randomized. The preparation and administration of the drugs were the same and the investigator and participants were blinded to the patients' group.

Suggestion

We suggest further studies with a larger sample size. Also, to determine the best sedative drug, it is better to compare lorazepam with other benzodiazepines. In addition, further studies can be done to compare multiple doses of lorazepam and different routes of administration. Moreover, evaluation of anxiety and stress in addition to sedative effects is suggested.

Conclusion

In this study, we examined the effects of 2 mg sublingual lorazepam as premedication in patients undergoing endoscopy. Lorazepam could be used as premedication in patients undergoing endoscopy without any considerable side effects.

Declarations

Ethics approval and consent to participate

This study was approved by the Research Council and Ethics Committee of the Hamadan University of Medical Sciences with the ethics code of IR.UMSHA.REC.1395.347. It was also registered on the website of the Iranian Registry of Clinical Trials (IRCT) with the following Number: IRCT201611039014N130; (05/11/2016); https://en.irct.ir/trial/9568. All participants were informed about the study protocol, and the probable beneficial or side effects of the drug, and signed the informed consent.

Consent for publication

Consent for publication The patients provided informed consent for the anonymous publication of their medical data and images.

Author contributions

Maryam Hasanzarrini: Conceptualization; Methodology; Project administration; Supervision; Writing – review & editing.

Samira Nirumandi Jahromi: Investigation; Writing – review & editing.

Amir Mohammad Salehi: Data curation; Investigation; Writing – original draft; Writing – review & editing.

Sara Ataei: Conceptualization.

Zohreh Seyfi: Formal analysis; Software; Writing – review & editing.

Jalal Poorolajal: Formal analysis; Software; Writing – review & editing.

Acknowledgements
None.

Funding
The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was funded by Hamadan University of Medical Science, Hamadan, Iran (951126764).

Competing interests
The authors declare that there is no conflict of interest.

Availability of data and materials
The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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References

1. Lin Y, Zhang X, Li L, *et al*. High-flow nasal cannula oxygen therapy and hypoxia during gastroscopy with propofol sedation: a randomized multicenter clinical trial. *Gastrointest Endosc* 2019; 90: 591–601.
2. Pambianco DJ and Cash BD. New horizons for sedation: the ultrashort acting benzodiazepine remimazolam. *Tech Gastrointest Endosc* 2016; 18: 22–28.
3. Mamula P, Markowitz JE, Neiswender K, *et al*. Safety of intravenous midazolam and fentanyl for pediatric GI endoscopy: prospective study of 1578 endoscopies. *Gastrointest Endosc* 2007; 65: 203–210.
4. Hua S. Advances in nanoparticulate drug delivery approaches for sublingual and buccal administration. *Front Pharmacol* 2019; 10: 1328.
5. Ulmer BJ, Hansen JJ, Overley CA, *et al*. Propofol versus midazolam/fentanyl for outpatient colonoscopy: administration by nurses supervised by endoscopists. *Clin Gastroenterol Hepatol* 2003; 1: 425–432.
6. Chennou F, Bonneau-Fortin A, Portolese O, *et al*. Oral lorazepam is not superior to placebo for lowering stress in children before digestive endoscopy: a double-blind, randomized, controlled trial. *Pediatr Drugs* 2019; 21: 379–387.
7. Çiçek SS. Structure-dependent activity of natural GABA (A) receptor modulators. *Molecules* 2018; 23: 1512.
8. Gress T, Miller M, Meadows C III, *et al*. Benzodiazepine overuse in elders: defining the problem and potential solutions. *Cureus* 2020; 12(10): e11042. DOI 10.7759/cureus.11042.
9. Maree RD, Marcum ZA, Saghafi E, *et al*. A systematic review of opioid and benzodiazepine misuse in older adults. *Am J Geriatr Psychiatry* 2016; 24: 949–963.
10. Shavakhi A, Soleiman S, Gholamrezaei A, *et al*. Premedication with sublingual or oral alprazolam in adults undergoing diagnostic upper gastrointestinal endoscopy. *Endoscopy* 2014; 46: 633–639.
11. Carson SS, Kress JP, Rodgers JE, *et al*. A randomized trial of intermittent lorazepam versus propofol with daily interruption in mechanically ventilated patients. *Crit Care Med* 2006; 34: 1326–1332.
12. Griffin CE, Kaye AM, Bueno FR, *et al*. Benzodiazepine pharmacology and central nervous system–mediated effects. *Ochsner J* 2013; 13: 214–223.
13. Ghiasi N, Bhansali RK and Marwaha R. *Lorazepam*. StatPearls [Internet]: StatPearls Publishing, 2023.
14. Van der Bijl P, Roelofse J and Joubert JdV. Comparison of sublingual lorazepam with intramuscular diazepam as sedatives during oral surgery. *J Oral Maxillofac Surg* 1988; 46: 559–568.
15. Thomson A, Andrew G and Jones DB. Optimal sedation for gastrointestinal endoscopy: review and recommendations. *J Gastroenterol Hepatol* 2010; 25: 469–478.
16. Telford J, Tavakoli I, Takach O, *et al*. Validation of the St. Paul's endoscopy comfort scale (SPECS) for colonoscopy. *J Canadian Assoc Gastroenterol* 2020; 3: 91–95.
17. Prajapati ST, Patel PB and Patel CN. Formulation and evaluation of sublingual tablets containing Sumatriptan succinate. *Int J Pharm Investig* 2012; 2: 162.

18. Varshosaz J, Firozian F and Ghassami E. Formulation, optimization and in vitro evaluation of rapid disintegrating and mucoadhesive sublingual tablets of lorazepam. *Farmacia* 2015; 63: 234–246.

19. Sebghatollahi V, Tabesh E, Gholamrezaei A, *et al*. Premedication with benzodiazepines for upper gastrointestinal endoscopy: comparison between oral midazolam and sublingual alprazolam. *J Res Med Sci* 2017; 22: 133.

20. Fihlman M, Karru E, Varpe P, *et al*. Feasibility of a transmucosal sublingual fentanyl tablet as a procedural pain treatment in colonoscopy patients: a prospective placebo-controlled randomized study. *Sci Rep* 2020; 10: 1–6.

21. Mula M. New non-intravenous routes for benzodiazepines in epilepsy: a clinician perspective. *CNS Drugs* 2017; 31: 11–17.

22. Weitz G, Homann N, von Jagow DC, *et al*. Premedication with orally administered lorazepam in adults undergoing ERCP: a randomized double-blind study. *Gastrointest Endosc* 2007; 66: 450–456.